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# A pilot study of temsirolimus and body composition

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## Abstract

**Purpose** Body weight and composition play a role in cancer etiology, prognosis, and treatment response. Therefore, we analyzed the weight, body composition changes, and outcome in patients treated with temsirolimus, an mTor inhibitor that has weight loss as one of its side effects.

**Patients and methods** Sixteen patients with advanced solid tumors treated with temsirolimus were studied; body composition was evaluated utilizing computerized tomography images. Sarcopenia was defined as skeletal muscle index lower than 38.5 cm<sup>2</sup>/m<sup>2</sup> for women and 52.4 cm<sup>2</sup>/m<sup>2</sup> for men.

**Results** Five of 16 patients (31 %) were men; median age, 60 years. Forty-four percent (7/16) of patients were sarcopenic. Fatigue, anemia, hyperglycemia, and hyperlipidemia were common. Baseline sarcopenia and body composition did not correlate with worse toxicity or treatment outcome. However, there was a trend for greater loss of adipose area ( $p=0.07$ ), fat mass ( $p=0.09$ ), and adipose index ( $p=0.07$ ) for patients with grade 3 or 4 toxicities versus those with grade 1 and 2 side effects.

**Conclusion** Patients with higher grade toxicities tended to lose more body fat, suggesting a possible end-organ metabolic effect of temsirolimus. These observations merit exploration in a larger cohort of patients.

**Keywords** Temsirolimus · Body composition · Sarcopenia · Toxicity

## 1 Introduction

Cancer treatment and cure remain a challenge to modern medicine; but recently, we have witnessed significant progress, especially in long-term disease control, transforming some cancer subtypes to a more chronic disease [1, 2]. More recently, there is an effort to personalize cancer treatment based on molecular aspects of the tumor, as well as the host characteristics [3, 4].

Body weight and body composition (fat and lean mass), are other features that play an important role in cancer etiology, prognosis, and treatment outcome [5, 6]. Body composition may also have significant impact on treatment-related toxicities, mainly for patients who are obese and/or have depletion of muscle mass, i.e., sarcopenia [5]. Sarcopenia may affect outcome by changing drug distribution and metabolism [7–9] and hence, personalizing and optimizing treatment might be enhanced by body composition measurements.

Cancer patients are at increased risk for sarcopenia because of the wasting syndrome (cachexia) that is a feature of many malignancies, having an incidence between 50–90 % of untreated patients [10]. Pancreatic and gastric malignancies are most frequently associated with weight loss greater than 5 % [11].

Temsirolimus is a mammalian target of rapamycin (mTor) inhibitor that has been approved by the US Food and Drug Administration for treatment of renal cell carcinoma [12]. Because it affects the phosphatidylinositol-3-kinase (PIK3)/AKT/mTor axis, it is conceivable that it may be useful in other tumors as well. Side effects including weight loss have been noted [12] and we have anecdotally observed failure to thrive in occasional patients with tumor regression. The mTor inhibition caused by temsirolimus affects other physiological processes linked to the PIK3/mTor/AKT pathway such as glucose, lipid, and protein metabolism. Pre-clinical data demonstrates that a catabolic state is associated with mTor inhibition [13–16], and relevant side effects seen with temsirolimus include hyperlipidemia and

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mucositis [17]. We therefore sought to analyze the association between body composition, including sarcopenia, and temsirolimus therapy.

## 2 Patients and methods

Twenty-six patients with documented advanced solid tumors (gynecological malignancies, non-small cell lung cancers, colorectal cancers, and others) who presented to the Clinical Center for Targeted Therapy (Phase I Clinic) at M.D. Anderson Cancer Center (MDACC) and who were enrolled on temsirolimus trial were studied. Inclusion criteria for the temsirolimus protocol were evaluable tumor(s) with documented PIK3 mutation and/or PTEN loss; patients with advanced/metastatic cancer that was refractory or relapsed after standard therapy, or had no standard therapy that improved survival by at least 3 months (unless temsirolimus was the standard treatment for that disease); creatinine  $\leq 3 \times$  upper limit of normal (ULN); absolute neutrophil count  $\geq 1,000/\text{mL}$ ; platelets  $\geq 50,000/\text{mL}$ ; and bilirubin  $\leq 3.0 \text{ g/dL}$  or  $\leq 5 \text{ ULN}$  if liver metastasis is present. Patients had to be off other anti-tumor agents for at least five half-lives or 4 weeks from the last day of treatment, whichever was shorter. For cytotoxic therapies, patients must have been at least 3 weeks off treatment. Patients could not be receiving any other experimental anti-tumor drugs. Exclusion criteria: pregnant or lactating women; known hypersensitivity to any of the components or metabolites of the drug products; and major surgery within 30 days prior to entering the study. Patients on inhibitors or inducers of CYP3A4 metabolism had the inhibitors or inducers stopped unless clinically contraindicated. The guidelines of the Internal Review Board at MDACC were followed for the temsirolimus protocol and the current body composition study.

### 2.1 Computed tomography imaging

Computed tomography (CT) images were performed at baseline (within 30 days before treatment) and were repeated every 2 cycles (about 8 weeks). Each cycle consisted of weekly 25 mg of temsirolimus intravenously for 4 weeks. The plan was that each patient would receive two treatment cycles before restaging. Tumor response was determined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. [18]

### 2.2 Demographic data

Demographic data (age, gender, cancer diagnosis, height, and weight) was collected from electronic medical records. Body weight was assessed at initiation of treatment and after two treatment cycles.

### 2.3 Toxicity data

Toxicity assessment was determined by review of electronic medical records and graded based on the Common Terminology Criteria for Adverse Events version 3.0. [19]. Patients were divided into two groups based on toxicity grade (grades 1–2 versus 3–4), since grade 3 or 4 toxicities likely would require dose reductions and treatment interruptions.

### 2.4 Laboratory data

Laboratory data was collected at baseline (within 7 days before the first treatment dose) and at the end of cycle two, which was within 7 days of the restaging scans. Complete blood counts, electrolytes, glucose, liver, and kidney profiles were accessed at baseline and at first restaging; lipid panel was evaluated at least once during the 8-week period.

### 2.5 Body composition assessments

Body mass index (BMI) was calculated with patient's weight (in kilograms) divided by height (in square meters) [20]. Lean body mass was calculated using the validated method described below.

Abdominal images at the level of the third lumbar vertebra (L3) were used for body composition analysis. The L3 CT cross-sectional image was chosen for analysis because it contains the following muscles: psoas, erector spinae, quadratus lumborum, transversus abdominis, rectus abdominis, and the external and internal oblique muscles, which together, are optimal for estimating lean body mass. The use of the L3 as the landmark for body composition analysis has been previously described and validated [21]. Muscle, intramuscular fat, subcutaneous fat, and visceral fat were identified by a single assessor trained in the specific anatomy of these tissues, demarcated using previously described Hounsfield unit thresholds [22] and quantified with sliceOmatic software, version 4.3 (TomoVision, Montreal, QC, Canada). Lean body mass (LBM) and fat body mass (FM) were estimated by the Mourtzakis et al. [23] formulae, ( $LBM(\text{kg}) = 0.30 \times \text{skeletal muscle at L3}(\text{cm}^2) + 6.06$  and  $FM(\text{kg}) = 0.042 \times \text{fat tissue at L3}(\text{cm}^2) + 11.2$ ), with demonstrated reliability ( $r = 0.94$ ,  $p < 0.0001$  and  $r = 0.88$ ,  $p < 0.0001$ , respectively). Patients were considered sarcopenic if they had a lumbar skeletal muscle index (skeletal muscle area at L3 divided by the height squared) lower than  $38.5 \text{ cm}^2/\text{m}^2$  for women and lower than  $52.4 \text{ cm}^2/\text{m}^2$  for men, as previously described [5]. Adipose index was determined by dividing adipose tissue area at L3 by the squared height.

## 2.6 Statistical analyses

Descriptive statistics were performed first to summarize our data. Differences in categorical variables were determined by Fisher's exact tests, where applicable. Differences in continuous variables were determined by *t* test or by the Mann–Whitney test, depending on the normality of the data. Analyses were performed using SPSS v. 19.0 (SPSS, Chicago, IL).

## 3 Results

### 3.1 Demography

From the initial 26 individuals, 17 patients (65 %) had restaging after 2 cycles and had body composition evaluated by the tomography method above. The remaining nine patients were not able to complete two treatment cycles; eight due to early progression, and one patient died in a car accident before restaging. One of the 17 patients had artifacts on imaging that compromised the evaluation. Therefore, the final study sample was 16 patients (11 women and five men). Median age was 60 years (range, 36–71 years). The most common tumor types were gynecological malignancies. Demographic data is summarized in Table 1.

**Table 1** Demographic characteristics of patients treated with temsirolimus, and assessable for body composition

Characteristics	Number
Gender	
Women (%)	11 (69)
Men (%)	5 (31)
Age, years	
Median (range)	60 (36–71)
Performance status (ECOG)	
<2 (%)	15 (94)
≥2 (%)	1 (6)
Cancer diagnoses	
Endometrial (%)	4 (25)
Ovarian (%)	3 (18)
Cervical (%)	2 (12)
Non-small cell, lung (%)	2 (12)
Colorectal (%)	2 (12)
Melanoma (%)	1 (6)
Squamous cell, anus (%)	1 (6)
Neuroendocrine (%)	1 (6)
Number of prior therapeutic regimens	
Median (range)	4 (1–11)

### 3.2 Anthropometric data

At baseline, two (12 %) patients were underweight (BMI <18.5 kg/m<sup>2</sup>), 10 (63 %) patients had normal weight (BMI=18.5–24.9 kg/m<sup>2</sup>), one (6 %) patient was overweight (BMI=25–29.9 kg/m<sup>2</sup>), and three (19 %) patients were obese (BMI ≥30 kg/m<sup>2</sup>). There were no significant changes in weight (*p*=0.87) and BMI (*p*=0.73) after two treatment cycles. The mean time between CT scans to assess body composition was 9 weeks. No significant changes in the median values of body composition parameters were identified; skeletal muscle area (SMA) (*p*=0.57), LBM (*p*=0.56), skeletal muscle index (SMI) (*p*=0.36), adipose area (AA) (*p*=0.65), FM (*p*=0.67), and adipose index (AI) (*p*=0.60).

Sarcopenia (SMI <38.5 cm<sup>2</sup>/m<sup>2</sup> for women and <52.4 cm<sup>2</sup>/m<sup>2</sup> for men) was a frequent finding, as is expected in cancer patients. There was no significant increase (*p*=0.72) in the prevalence of sarcopenia at baseline (7/16, 44 %) versus after two treatment cycles (9/16, 56 %). All patients that were sarcopenic at baseline remained sarcopenic after treatment. Two patients became sarcopenic after treatment—one man (SMI<sub>baseline</sub>=60.1 cm<sup>2</sup>/m<sup>2</sup> and SMI<sub>after treatment</sub>=48.1 cm<sup>2</sup>/m<sup>2</sup>) and one woman (SMI<sub>baseline</sub>=39.8 cm<sup>2</sup>/m<sup>2</sup> and SMI<sub>after treatment</sub>=35.7 cm<sup>2</sup>/m<sup>2</sup>). There was no difference in the median age between the sarcopenic and non-sarcopenic groups (63 and 62 years, *p*=0.75).

### 3.3 Toxicities

The most common toxicities, at least possibly drug-related, were fatigue (16/16, 100 %), anemia (16/16, 100 %), hyperglycemia (13/16, 81 %), and hypercholesterolemia (12/16, 75 %). The great majority of the toxicities were grade 1 or 2 (100/111, 90 %). Anemia, thrombocytopenia, leucopenia/neutropenia, and aspartate aminotransferase/alanine aminotransferase elevations were the only grade 3 or 4 toxicities.

#### 3.3.1 Baseline sarcopenia and toxicity

Baseline sarcopenia (i.e., SMI <38.5 cm<sup>2</sup>/m<sup>2</sup> for women and <52.4 cm<sup>2</sup>/m<sup>2</sup> for men) did not correlate with toxicity profile; the median number of toxicities per patient was seven (range 5–9) for both sarcopenic and non-sarcopenic patients (*p*=0.74). Grade 3 or 4 toxicities occurred in 3/7 sarcopenic patients and 3/9 non-sarcopenic patients at baseline.

#### 3.3.2 Baseline body composition and toxicity

Median values for body composition parameters at baseline among patients with grade 1 or 2 toxicity versus 3 or 4 were not significantly different (Table 2).

### 3.3.3 Body composition changes and toxicity after two treatment cycles

The body composition changes were estimated as a delta function:

$$\text{Delta body composition parameter} = \text{body composition parameter}_{\text{after treatment}} - \text{body composition parameter}_{\text{baseline}}$$

Changes in body composition parameters after two treatment cycles (about 8 weeks) were not significantly different between the grade 1 or 2 toxicity group and the grade 3 or 4 toxicity group; however, there was a trend for a greater loss of adipose area ( $p=0.07$ ), fat mass ( $p=0.09$ ), and adipose index ( $p=0.07$ ) for patients with grade 3 or 4 toxicity versus patients with grade 1 or 2 (Table 3).

### 3.4 Therapy response

#### 3.4.1 Baseline sarcopenia and response

Eleven patients had stable disease or partial response (SD/PR) and five patients had progressive disease (PD) after 2 months. Three out of seven sarcopenic (43 %) patients at baseline had PD after 2 months versus two out of nine non-sarcopenic (23 %) patients ( $p=0.60$ ). The average best response by RECIST criteria, after 2 months, was 18 % increase in tumor measurement for baseline sarcopenic patients and 5 % increase for baseline non-sarcopenic patients ( $p=0.20$ ) (Fig. 1).

#### 3.4.2 Baseline body composition and response

Median values of baseline body composition parameters were not significantly different for patients with SD/PR versus those with PD and are summarized in Table 2.

### 3.4.3 Body composition changes after two treatment cycles and response

Body composition parameters did not change significantly after 2 months when comparing the SD/PR group and the PD group (Table 3).

### 3.5 Toxicity and therapy response

Four (36 %) out of 11 patients with SD/PR had grade 3 or 4 toxicity versus two (40 %) out of five patients with PD ( $p=1.00$ ).

## 4 Discussion

Temsirolimus is an antineoplastic agent, which acts predominantly by inhibiting the mTor kinase. It has a gastrointestinal toxicity profile that includes mucositis, nausea, and anorexia. Therefore, it would be expected that patients on treatment with this agent could lose weight [12]. Temsirolimus also affects lipid profile and metabolism [17] and all these mechanisms may account for the fact that about 19 % of patients showed significant weight loss [12].

The mTor pathway is a key signaling for cell proliferation making it an important target for cancer therapy [12, 24]. However, there are other physiological processes that also depend on this pathway, such as protein synthesis, insulin signaling, and lipid metabolism [15, 25], and all of these might impact body composition. Pre-clinical data have demonstrated that activation of PIK3/mTor/AKT pathway plays an important role on muscle skeletal trophism, inducing hypertrophism, inhibiting muscle atrophy, and inducing lipogenesis [13, 14]. In animal models, chronic treatment with rapamycin caused glucose intolerance and reduced the number

**Table 2** Body composition parameters at baseline and relation to toxicity and to therapy response by RECIST criteria after two treatment cycles

Median (IQR)	Toxicity			Response		
	Grade 1 or 2 toxicity <i>n</i> =10	Grade 3 or 4 toxicity <i>n</i> =6	<i>p</i> Value	SD/PR <i>n</i> =11	PD <i>n</i> =5	<i>p</i> Value
Total <i>n</i> =16						
Weight(kg)	65.8 (23.5)	54.9 (27.3)	0.59	62.7 (23.3)	59.1 (29.1)	0.46
BMI (kg/m <sup>2</sup> )	21.5 (9.9)	20.5 (4.4)	0.28	21.2 (9.9)	21.2 (3.3)	0.53
SMA (cm <sup>2</sup> )	128.1 (46)	107.4 (32.3)	0.28	125.5 (30.4)	103.5 (48.7)	0.69
LBM (kg)	44.5 (13.8)	38.3 (9.7)	0.28	43.7 (9.1)	37.1 (14.6)	0.69
SMI (cm <sup>2</sup> /m <sup>2</sup> )	45.1 (13.9)	39.7 (3.8)	0.59	44.2 (12.5)	39.8 (5.2)	0.46
AA (cm <sup>2</sup> )	149.3 (217.3)	166.7 (216.6)	0.66	164.4 (242.8)	147.3 (132.9)	0.61
FM (kg)	17.5 (9.1)	18.2 (9.1)	0.63	18.1 (10.2)	17.4 (5.5)	0.57
AI (cm <sup>2</sup> /m <sup>2</sup> )	48.4 (78.0)	58.3 (82.5)	0.87	49.1 (83.6)	47.7 (34.1)	0.57

AA adipose area, AI adipose index, FM fat mass, IQR interquartile range, LBM lean body mass, PD: progressive disease, PR partial response, SD stable disease, SMA skeletal muscle area, SMI skeletal muscle index

**Table 3** Body composition changes after two treatment cycles and relation with toxicity and therapy response per RECIST criteria

Variable, median (IQR)	Toxicity			Response		
	Grade 1/2 <i>n</i> =10	Grade 3/4 <i>n</i> =6	<i>p</i> Value	SD/PR <i>n</i> =11	PD <i>n</i> =5	<i>p</i> Value
<i>n</i> =16						
Δ Weight (kg)	−0.8 (5.4)	−1.5 (6.2)	0.79	−0.8 (5.3)	−0.8 (5.9)	0.78
Δ BMI (kg/m <sup>2</sup> )	−0.4 (1.9)	−0.6 (2.4)	0.87	−0.4 (1.9)	−0.3 (2.1)	0.74
Δ SMA (cm <sup>2</sup> )	−3.5 (11.4)	−6.6 (16.0)	0.66	−5.0 (17.0)	0.9 (13.8)	0.31
Δ LBM (kg)	−1.1 (3.4)	−2.0 (4.8)	0.66	−1.5 (5.1)	0.3 (4.2)	0.31
Δ SMI (cm <sup>2</sup> /m <sup>2</sup> )	−1.4 (3.9)	−2.2 (6.5)	0.66	−2.0 (5.6)	0.4 (4.8)	0.34
Δ AA (cm <sup>2</sup> )	−12.3 (52.0)	−32.8 (30.2)	0.07	−18.2 (44.5)	−30.4 (31.9)	0.33
Δ FM (kg)	−0.6 (2.2)	−1.4 (1.2)	0.09	−0.8 (1.9)	−1.3 (1.4)	0.33
Δ AI (cm <sup>2</sup> /m <sup>2</sup> )	−4.5 (18.2)	−13.5 (11.9)	0.07	−6.3 (16.9)	−10.9 (10.1)	0.40

Δ refers to median value of each body composition parameter after treatment – median value before treatment

AA adipose area, AI adipose index, FM fat mass, IQR interquartile range, LBM lean body mass, PD progressive disease, PR partial response, SMA skeletal muscle area, SD stable disease, SMI skeletal muscle index

of adipose cells, impairing lipid deposition on adipose tissue and culminating in elevated plasma levels of triglycerides [16]. In the clinical setting, hyperlipidemia and hyperglycemia are features of temsirolimus and other mTor inhibitors-side effects [12]. Recently, Antoun et al. [26] demonstrated that muscle loss is specifically exacerbated by sorafenib in patients with renal cell carcinoma, possibly related to the downstream inhibition of PIK3/AKT/mTor pathway, confirming the pre-clinical models.

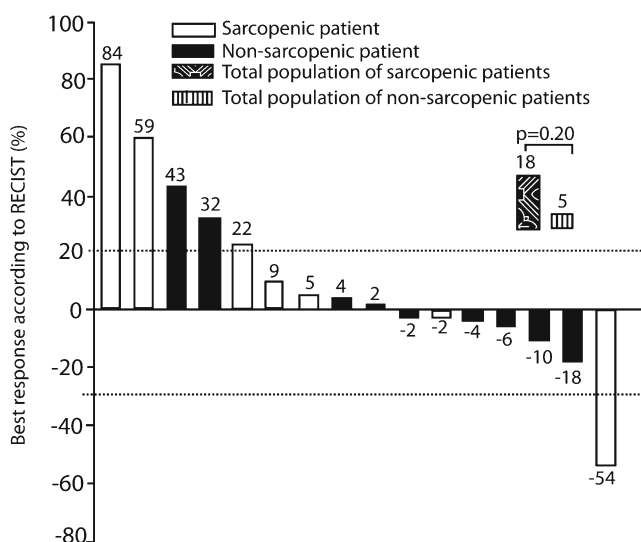
Our analyses did not show a significant overall decrease in weight, BMI, or other body composition parameters in the first 2 months, which could be explained by the fact that all patients with anorexia, nausea, and/or mucositis had only grade 1 or 2 toxicities, and/or might be because the follow-up of our study was not long enough to detect such changes. The

small number of patients might also preclude finding statistically significant changes.

Sarcopenia, as reflected by SMI, was found in 7/16 patients (44 %) in our study population (3/11 women and 4/5 men) in concordance with other studies. Our previous report showed sarcopenia in 51 % in a group of 104 patients with diverse solid tumors referred to our Phase I Clinic [27]. Tan et al. [28] found a prevalence of sarcopenia in 56 % of 111 patients with advanced pancreatic cancer, and Prado et al. [7] found sarcopenia in 25 % of women with metastatic breast cancer.

Previous reports have shown that sarcopenia and low lean body mass had a significant impact on toxicity, more specifically in the incidence of grade 3 or 4 toxicities, for patients treated with chemotherapy (5-fluoracil, cyclophosphamide, methotrexate, and capecitabine) or target agents such as sorafenib [7–9, 29]. From our analyses, patients who were sarcopenic at baseline did not have increase in grade 3 or 4 toxicities. Patients who developed grade 3 or 4 toxicities had a lower SMI at baseline, but the difference was not statistically significant when compared to the group with grade 1 or 2 toxicities.

After treatment, individual body composition variables did not change in a statistically significant fashion. However, there was a trend for a greater decrease of body fat parameters after treatment in patients with grade 3 or for toxicity ( $p=0.07$ ). These results may suggest that patients who lose body fat are more vulnerable to grade 3 or 4 temsirolimus-related toxicities. Alternatively, developing grade 3 or 4 toxicities and a decrease in fat mass may be related to greater end-organ impact or higher blood levels of temsirolimus in these patients. Recently, several studies have addressed the relationship between body composition and targeted therapy, especially anti-angiogenesis agents. Renal carcinomas are of

**Fig. 1** Sarcopenia data and response to RECIST



special interest because obesity may be a known risk factor for development of this malignancy [30], and anti-angiogenesis agents, as well as mTor inhibitors, are currently the back-bone of standard therapy. Body fat content, until recently, demonstrated very little evidence of impacting survival and toxicity [26]. However, Steffens et al. [31, 32] showed that increased body fat was related with longer survival for patients with renal cell carcinoma treated with VEGF-targeted therapy. On the other hand, Ladoire et al. [32, 33] showed that increase in visceral fat was correlated with shorter overall survival in patients with renal cell carcinoma. Therefore, our understanding of the complex interaction between cancer and the host's characteristics is incomplete, but may be especially relevant to targeted agents with metabolic effects.

There are several limitations to our study. These are preliminary findings of a pilot study. The low number of patients and the short follow-up period preclude a robust statistical analysis. In conclusion, we could not demonstrate an impact of temsirolimus on skeletal muscle content like others have shown for other targeted agents [26], however our results suggest that patients treated with an mTor inhibitor who develop grade 3 or 4 toxicities tend to lose more body fat content than those with only grade 1 or 2 toxicities. Our observations are hypothesis generating and merit exploration in a larger cohort of patients.

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**Conflict of interest** The authors declare that they have no conflict of interest.

## References

- Slamon DJ et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783–92.
- Verweij J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*. 2004;364:1127–34.
- Kwak EL et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363:1693–703.
- Chapman PB et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507–16.
- Prado CM et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9:629–35.
- Murthy NS et al. Dietary factors and cancer chemoprevention: an overview of obesity-related malignancies. *J Postgrad Med*. 2009;55:45–54.
- Prado CM et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res*. 2009;15:2920–6.
- Aslani A et al. The predictive value of body protein for chemotherapy-induced toxicity. *Cancer*. 2000;88:796–803.
- Prado CM et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res*. 2007;13:3264–8.
- Dewys WD et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med*. 1980;69:491–7.
- Tisdale MJ. Cancer cachexia. *Curr Opin Gastroenterol*. 2010;26:146–51.
- Hudes G et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356:2271–81.
- Bodine SC et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol*. 2001;3:1014–9.
- McCarthy JJ, Esser KA. Anabolic and catabolic pathways regulating skeletal muscle mass. *Curr Opin Clin Nutr Metab Care*. 2010;13:230–5.
- Laplane M, Sabatini DM. An emerging role of mTOR in lipid biosynthesis. *Curr Biol*. 2009;19:R1046–52.
- Houde VP et al. Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue. *Diabetes*. 2010;59:1338–48.
- Bhojani N et al. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol*. 2008;53:917–30.
- Therasse P et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205–16.
- Trotti A et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13:176–81.
- Billewicz WZ, Kemsley WF, Thomson AM. Indices of adiposity. *Br J Prev Soc Med*. 1962;16:183–8.
- Mitsiopoulos N et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol*. 1998;85:115–22.
- Shen W et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol*. 2004;97:2333–8.
- Mourtzakis M et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33:997–1006.
- Yao JC et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514–23.
- Vogt PK. PI 3-kinase, mTOR, protein synthesis and cancer. *Trends Mol Med*. 2001;7:482–4.
- Antoun S et al. Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. *J Clin Oncol*. 2010;28:1054–60.

27. Parsons HA et al. Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service. *PLoS One*. 2012;7:e29330.
28. Tan BH et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res*. 2009;15:6973–9.
29. Antoun S et al. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol*. 2010;21:1594–8.
30. Chow WH et al. Obesity and risk of renal cell cancer. *Cancer Epidemiol Biomark Prev*. 1996;5:17–21.
31. Steffens S et al. Does obesity influence the prognosis of metastatic renal cell carcinoma in patients treated with vascular endothelial growth factor-targeted therapy? *Oncologist*. 2011;16:1565–71.
32. Tang PA, Heng DY, Choueiri TK. Impact of body composition on clinical outcomes in metastatic renal cell cancer. *Oncologist*. 2011;16:1484–6.
33. Ladoire S et al. Visceral fat area as a new independent predictive factor of survival in patients with metastatic renal cell carcinoma treated with antiangiogenic agents. *Oncologist*. 2011;16:71–81.